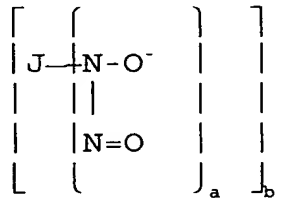
PENDING CLAIMS
U.S. SERIAL NO. 08/837,812

BIOPOLYMER-BOUND NITRIC OXIDE-RELEASING COMPOSITIONS, PHARMACEUTICAL COMPOSTIONS INCORPORATING SAME AND METHODS OF TREATING BIOLOGICAL DISORDERS USING SAME

1. A polymeric composition capable of releasing nitric oxide, said composition comprising (i) a biopolymeric backbone wherein said backbone is of a tissue-specific antibody or fragment thereof, a cell-specific antibody or fragment thereof, a tumor-specific antibody or fragment thereof, a protein containing a recognition sequence for a receptor-ligand interaction favorable to cell or tissue selective attachment, wherein said backbone includes at least one amino group or at least one carboxyl group or combinations thereof, and (ii) at least one nitric oxide-releasing $N_2O_2^-$ functional group selected from the group consisting of X-[N(O)NO] and [N(O)NO]-X, wherein X is a nucleophilic or electrophilic organic residue covalently bonded to said $N_2O_2^-$ functional group, and wherein the $N_2O_2^-$ functional group is covalently bound to said polymeric composition at one or more of said amino group or said carboxyl group through said nucleophilic or electrophilic organic residue.

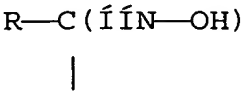
5. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



(I)

wherein J is an inorganic moiety or an organic moiety selected from the group consisting of C_1-C_{12} aliphatic, C_3-C_8 cycloalkyl, benzyl, phenyl, substituted benzyl, substituted phenyl,

benzylcarbonyl, phenylcarbonyl, substituted benzylcarbonyl, substituted phenylcarbonyl, C_1-C_{12} acyl, and

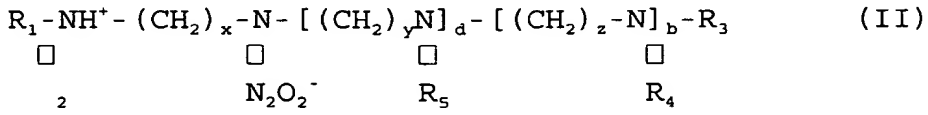


wherein R is C_1-C_{12} aliphatic, C_3-C_8 cycloalkyl, benzyl, phenyl, substituted benzyl or substituted phenyl, and said substituted benzyl and substituted phenyl is substituted with one or two substituents selected from the group consisting of halogen, hydroxy, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkyl-amino, phenyl and phenoxy, M^{+x} is a pharmaceutically acceptable cation, where x is the valence of the cation, a is one or two, and b and c are the smallest integers that result in a neutral compound.

6. The method of claim 5, wherein J is a moiety which is linked to the nitrogen of the remainder of the complex through an atom other than a carbon atom.

7. The polymeric composition of claim 5, wherein the nitric-oxide releasing group is a compound other than a salt of alanosine or dopastin.

8. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:

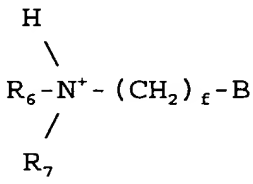


(II)

wherein b and d are the same or different and may be zero or one, R_1, R_2, R_3, R_4, and R_5 are the same or different and may be

hydrogen, C_{3-8} cycloalkyl, C_{1-12} straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, and x, y, and z are the same or different and are integers from 2 to 12.

9. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



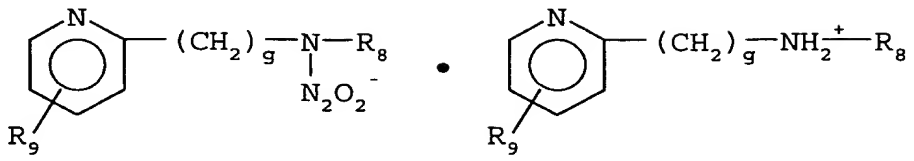
(III)

wherein B is $N_2O_2^-$ or $N_2O_2^-$,

R_6 and R_7 are the same or different and may be hydrogen, C_{3-8} cycloalkyl, C_{1-12} straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, f is an integer from 0 to 12, with the proviso that when B is the substituted piperazine moiety

then f is an integer from 2 to 12.

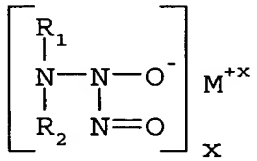
10. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



(IV)

wherein R_8 is hydrogen, C_{3-8} cycloalkyl, C_{1-12} straight or branched chain alkyl, benzyl, benzoyl, phthaloyl, acetyl, trifluoroacetyl, p-toluyl, t-butoxycarbonyl, or 2,2,2-trichloro-t-butoxycarbonyl, R_9 is hydrogen or a C_1-C_{12} straight or branched chain alkyl, and g is 2 to 6.

11. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:



(V)

wherein R_1 and R_2 are independently selected from the group consisting of a straight chain or branched chain C_1 - C_{12} alkyl group and a benzyl group, or else R_1 and R_2 together with the nitrogen atom they are bonded to form a heterocyclic group, a pyrrolidino, piperidino, piperazino or morpholino group, M^{+x} is a pharmaceutically acceptable cation, and x is the valence of the cation.

12. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:

$$K[(M)_x^{x'}(L)_y(R^1R^2N\text{-}N_2O_2)_z] \qquad (VI)$$

wherein M is a pharmaceutically acceptable metal, or, where x is at least two, a mixture of two different pharmaceutically acceptable metals, L is a ligand different from $(R^1R^2N\text{-}N_2O_2)$ and is bound to at least one metal, R^1 and R^2 are each organic moieties and may be the same or different, x is an integer of from 1 to 10, x' is the formal oxidation state of the metal M, and is an integer of from 1 to 6, y is an integer of from 1 to 18, and where y is at least 2, the ligands L may be the same or different, z is an integer of from 1 to 20, and K is a pharmaceutically acceptable counterion to render the compound neutral to the extent necessary.

13. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:

$$[R\text{-}N(H)N(NO)O\text{-}]_yX \qquad (VII)$$

wherein R is $C_{2\text{-}8}$ lower alkyl, phenyl, benzyl, or $C_{3\text{-}8}$ cycloalkyl, any of which R groups may be substituted by one to three substituents, which are the same or different, selected from the group consisting of halo, hydroxy, $C_{1\text{-}8}$ alkoxy, $-NH_2$, $-C(O)NH_2$, $-CH(O)$, $-C(O)OH$, and $-NO_2$, X is a pharmaceutically acceptable cation, a pharmaceutically acceptable metal center, or a pharmaceutically acceptable organic group selected from the group consisting of $C_{1\text{-}8}$ lower alkyl, $-C(O)CH_3$, and $-C(O)NH_2$, and y is one to three, consistent with the valence of X.

14. The polymeric composition of claim 1, wherein said nitric oxide-releasing $N_2O_2^-$ functional group is of the formula:

$$R_1R_2N\text{-}N(\square)\rightarrow O \qquad \text{(VIII)}$$

wherein R_1 and R_2 are independently chosen from $C_{1\text{-}12}$ straight chain alkyl, $C_{1\text{-}12}$ alkoxy or acyloxy substituted straight chain alkyl, $C_{2\text{-}12}$ hydroxy or halo substituted straight chain alkyl, $C_{3\text{-}12}$ branched chain alkyl, $C_{3\text{-}12}$ hydroxy, halo, alkoxy, or acyloxy substituted branched chain alkyl, $C_{3\text{-}12}$ straight chain olefinic and $C_{3\text{-}12}$ branched chain olefinic which are unsubstituted or substituted with hydroxy, alkoxy, acyloxy, halo or benzyl, or R_1 and R_2 together with the nitrogen atom to which they are bonded form a heterocyclic group, a pyrrolidino, piperidino, piperazino or morpholino group, and R_3 is a group selected from $C_{1\text{-}12}$ straight chain and $C_{3\text{-}12}$ branched chain alkyl which are unsubstituted or substituted by hydroxy, halo, acyloxy or alkoxy, $C_{2\text{-}12}$ straight chain or $C_{3\text{-}12}$ branched chain olefinic which are unsubstituted or substituted by halo, alkoxy, acyloxy or hydroxy, $C_{1\text{-}12}$ unsubstituted or substituted acyl, sulfonyl and carboxamido; or R_3 is a group of the formula $-(CH_2)_n\text{-}ON{=}N(O)NR_1R_2$, wherein n is an integer of 2-8, and R_1 and R_2 are as defined above; with the proviso that R_1, R_2 and R_3 do not contain a halo or a hydroxy substituent α to a heteroatom.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 1.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 5.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 6.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 7.

22. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 8.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 9.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 10.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 11.

26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the polymeric composition of claim 12.

27. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering to said mammal a polymeric composition capable of releasing nitric oxide, said composition comprising

a biopolymeric backbone wherein said backbone is a protein, wherein said backbone includes at least one amino group or at least one carboxyl group or combinations thereof, and a nitric oxide-releasing $N_2O_2^-$ functional group selected from the group consisting of X-[N(O)NO] and [N(O)NO]-X, wherein X is a nucleophilic or electrophilic organic residue covalently bonded to said $N_2O_2^-$ functional group, and wherein the $N_2O_2^-$ functional group is covalently bound to said biopolymer at one or more of said amino group or said carboxyl group in an amount sufficient to release a therapeutically effective amount of nitric oxide.

31. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 5 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

32. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 6 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

33. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 7 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

34. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 8

in an amount sufficient to release a therapeutically effective amount of nitric oxide.

35. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 9 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

36. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 10 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

37. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 11 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

38. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering the polymeric composition of claim 12 in an amount sufficient to release a therapeutically effective amount of nitric oxide.

39. A method of treating a biological disorder in a mammal in which dosage with nitric oxide is therapeutic, comprising administering to said mammal the polymeric composition of claim 1 in an amount sufficient to release a therapeutically effective amount of nitric oxide.